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United States Patent [19]**Bagchi et al.**[11] **Patent Number:** **5,662,883**[45] **Date of Patent:** ***Sep. 2, 1997**[54] **MICROPRECIPITATION OF MICRO-NANOPARTICULATE PHARMACEUTICAL AGENTS**[75] **Inventors:** **Pranab Bagchi**, Webster; **Robert C. Stewart**, Spencerport, both of N.Y.; **Gregory L. McIntire**, West Chester, Pa.; **John R. Minter**, Rochester, N.Y.[73] **Assignee:** **NanoSystems L.L.C.**, Collegeville, Pa.[*] **Notice:** The term of this patent shall not extend beyond the expiration date of Pat. No. 5,560,932.[21] **Appl. No.:** **370,936**[22] **Filed:** **Jan. 10, 1995**[51] **Int. Cl.⁶** **A61K 9/14; A61K 49/04**[52] **U.S. Cl.** **424/9.4; 424/489; 424/490; 424/488; 424/9.5**[58] **Field of Search** **424/9.4, 9.51, 424/450, 489, 499, 455, 488, 9.5**[56] **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Gary E. Hollinden*Assistant Examiner*—Michael G. Hartley*Attorney, Agent, or Firm*—Rudman & Balogh[57] **ABSTRACT**

It has been known that administration of pharmaceutical agents (both diagnostic and therapeutic) with poor water solubility in the form of particles less than 400 nm in diameter produces agent formulation with increased bioavailability. Bioavailability being proportional to the surface area, increases with reduction of particle size of the dispersed agent. We have discovered that chemical derivatization of certain photographic coupler molecules with chemical moiety that are capable of functioning as pharmaceutical agents (both diagnostic and therapeutic) is amenable to the preparation of nanoparticulate pharmaceutical agent dispersions via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of a suitable surface-modifying, surface-active agent to form an ultra fine particle dispersion of the said pharmaceutical agent. The composition and process of this invention leads to particles of Z-average diameters as small as up to 10 nm as measured by photon correlation spectroscopy. The composition and process schemes of this invention are suitable for large-scale manufacture of these micro-nanoparticulate pharmaceutical agent dispersions.

53 Claims, 11 Drawing Sheets